Drug Class Review

Beta Adrenergic Blockers

Final Report Update 4
Executive Summary

July 2009

Update 3: September 2007
Update 2: May 2005
Update 1: September 2004
Original Report: September 2003

The literature on this topic is scanned periodically.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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INTRODUCTION

Beta blockers inhibit the chronotropic, inotropic, and vasoconstrictor responses to the catecholamines, epinephrine, and norepinephrine. Most beta blockers have half-lives of over 6 hours (Table 1). The shortest acting are pindolol (3 to 4 hours) and propranolol (3 to 5 hours). Most of the included beta blockers are metabolized in combination by the liver and kidneys, with the exception of atenolol, which is metabolized primarily by the kidneys while the liver has little to no involvement.

The beta blockers listed in Table 1 are approved for the treatment of hypertension. Other Food and Drug Administration approved uses are specific to each beta blocker and include stable and unstable angina, arrhythmias, bleeding esophageal varices, coronary artery disease, asymptomatic and symptomatic heart failure, hypertension migraine, and secondary prevention post-myocardial infarction.

Beta blockers differ in their effects on the 3 adrenergic receptors (β_1, β_2, and α) and in their duration of effect (Table 1). Cardioselective beta blockers preferentially inhibit β_1 receptors that are principally found in the myocardium. Non-cardioselective beta blockers also inhibit β_2 receptor sites, which are found in smooth muscle in the lungs, blood vessels, and other organs. Beta blockers with intrinsic sympathomimetic activity act as partial adrenergic agonists and would be expected to have less bradycardic and bronchoconstriction effects than other beta blockers. Finally, carvedilol and labetalol block α-adrenergic receptors and would be expected to reduce peripheral vascular resistance more than other beta blockers.

Table 1. Beta blockers included in the review

Drug	Usual hypertension dose	Daily dosing frequency	Half-life (hours)	Cardio-selective	Partial agonist activity (ISA)	Alpha antagonist effect
Acebutolol	200-1200 mg/d	Twice	3-4	Yes	Yes	No
Atenolol	50-100 mg/d	Once	6-9	Yes	No	No
Betaxolol	5-40 mg/d	Once	14-22	Yes	No	No
Bisoprolol	5-20 mg/d	Once	9-12	Yes	No	No
Carteolol	2.5-10 mg/d	Once	6	No	Yes	No
Carvedilol	12.5-50 mg/d	Twice	7-10	No	No	Yes
Carvedilol phosphate (controlled release)	20-80 mg/d	Once	10.6-11.5	No	No	Yes
Labetalol	200-1200 mg/d	Twice	3-6	No	No	Yes
Metoprolol tartrate	50-200 mg/d	Twice	3-7	Yes	No	No
Metoprolol succinate (extended release)	50-400 mg/d	Once	3-7	Yes	No	No
Nadolol	20-240 mg/d	Once	10-20	No	No	No
Nebivolol	5-40 mg/d	Once	12-19	Yes	No	No
Penbutolol	20 mg/d	Once	5	No	Yes	No
Pindolol	10-60 mg/d	Twice	3-4	No	Yes	No
Propranolol	40-240 mg/d	Twice	3-4	No	No	No
Propranolol long-acting	60-240 mg/d	Once	8-11	No	No	No
Timolol	10-40 mg/d	Twice	4-5	No	No	No

Abbreviations: d, day; ISA, intrinsic sympathomimetic activity.

Scope and Key Questions

The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. Initially, the Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed, revised, and approved by representatives of organizations participating in the Drug Effectiveness Review Project. It is the representatives' responsibility to ensure that the questions reflect public input or input from their members. The participating organizations approved the following key questions to guide this review.

Key Question 1. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in effectiveness/efficacy?

Key Question 2. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine prophylaxis or bleeding esophageal varices, do beta blocker drugs differ in harms?

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

For studies of hypertension, we excluded studies in which blood pressure lowering was the only endpoint; most of these studies seek to identify equivalent doses of beta blockers rather than differences in clinical effectiveness. Instead, we sought evidence of long-term effects on mortality, cardiovascular events, and quality of life. We only included studies in stable angina patients with duration of 2 months or longer. We only included studies of long-term treatment in post-coronary artery bypass graft patients, excluding studies of the short-term use of beta blockers to suppress atrial arrhythmias. With regard to placebo-controlled trials of recent myocardial infarction or heart failure, we only included studies with sample sizes of 100 patients or more.

We included the following safety outcomes: overall adverse event incidence, withdrawals due to adverse events, and frequency of important adverse events associated with beta blockers including bradycardia, heart failure, and hypotension. In some studies, only "serious" or "clinically significant" adverse events are reported. Some studies do not define these terms, and in other studies, the definitions vary between studies.

To evaluate efficacy, we included randomized controlled trials and good-quality systematic reviews. To evaluate effectiveness and safety, we included trials as well as good-quality observational studies.

METHODS

To identify relevant citations, we searched Ovid MEDLINE (1966 to January Week 4 2009), the Cochrane Database of Systematic Reviews (Second Quarter 2008), Database of Abstracts of Reviews of Effects (Third Quarter 2008) and the Cochrane Central Register of Controlled Trials (Third Quarter 2008), using terms for included drugs, indications, and study designs (see Appendix B for complete search strategies). In addition, pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote® 9.0).

We assessed the internal validity (quality) of trials based on predefined criteria that are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK) criteria. We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis.

RESULTS

Searches identified 6325 citations, with 606 new in Update 4. Dossiers were received for Update 4 from the manufacturers of carvedilol, carvedilol controlled release, and nebivolol.

Key Question 1. Do beta blocker drugs differ in efficacy or effectiveness?

Key Question 1a. For adult patients with hypertension, do beta blockers differ in efficacy or effectiveness?

Direct comparisons

There were no head-to-head trials of different beta blockers on long-term (≥6 months) health or quality of life outcomes. Beta blockers are equally efficacious in controlling blood pressure in patients with hypertension. No beta blocker has been demonstrated to be more efficacious or to result in better quality of life than other beta blockers, either as initial therapy or when added to a diuretic, ACE inhibitor, or ARB.

Placebo-controlled and active control trials

Evidence from long-term trials is mixed; overall, beta blockers are generally less effective than diuretics, and usually no better than placebo, in reducing cardiovascular events. The exception was 1 large trial in which treatment with metoprolol resulted in lower all-cause mortality than treatment with a thiazide diuretic.

Key Question 1b. For adult patients with angina, do beta blockers differ in efficacy or effectiveness?

Direct comparisons

There were no differences in exercise tolerance or attack frequency in head-to-head trials of carvedilol compared with metoprolol, pindolol compared with propranolol, betaxolol compared with propranolol, and betaxolol compared with metoprolol tartrate in patients with chronic stable angina. Atenolol and bisoprolol were equivalent in angina patients with chronic obstructive pulmonary disease. Atenolol and labetalol (when combined with chlorthalidone) were equivalent in angina patients with hypertension. Beta blockers that had intrinsic sympathomimetic activity reduced the resting heart rate less than other beta blockers, a potential disadvantage in patients suffering from angina pectoris. For this reason, experts recommend against using beta blockers with *intrinsic sympathomimetic activity* in patients with angina.

Placebo-controlled trials

One short-term, placebo-controlled trial of propranolol did not add any meaningful evidence of comparative efficacy in attack frequency or exercise parameters.

Key Question 1c. For adult patients who have undergone coronary artery bypass grafting, do beta blockers differ in efficacy or effectiveness?

Direct comparisons

We found no head-to-head trials of beta blockers in adults following coronary artery bypass graft.

Placebo-controlled trials

In 7 trials, long-term use of a beta blocker after coronary artery bypass graft did not improve mortality or other outcomes. For example, the MACB Study Group conducted a fair quality trial that randomized 967 patients (85.5% male, median age 64 years) to metoprolol 200 mg once daily or placebo within 5 to 21 days following coronary artery bypass graft and measured the effects of treatment on death and cardiac events. No differences between metoprolol and placebo were found in mortality (3.3% compared with 1.8%; P=0.16) or in ischemic events (myocardial infarction, unstable angina, need for additional coronary artery bypass graft or percutaneous transluminal coronary angioplasty).

Key Question 1d. For adult patients with recent myocardial infarction, do beta blockers differ in efficacy or effectiveness?

Direct comparisons

No consistent differences between beta blockers were found in 3 head-to-head trials in postmyocardial infarction patients. One fair-quality head-to-head trial found no differences in mortality after 1 year between atenolol and propranolol, but this was a relatively small trial. One fair-quality head-to-head trial found no differences in time to serious cardiovascular events between carvedilol and atenolol. One fair-quality head-to-head trial found no differences in time to first cardiac adverse event or all-cause mortality between carvedilol and metoprolol tartrate.

Placebo-controlled trials

In placebo-controlled trials, similar mortality reductions were reported for acebutolol, metoprolol tartrate, propranolol, and timolol for patients following myocardial infarction without other complications. Similar reductions in sudden death and reinfarction were reported for metoprolol tartrate and timolol and in sudden death for propranolol. Carvedilol is the only beta blocker shown to reduce mortality in post-myocardial infarction patients who are already taking an ACE inhibitor. No studies of carvedilol phosphate (extended-release carvedilol) in patients with recent myocardial infarction were identified. Carvedilol reduced mortality and reinfarction in 1 placebo-controlled trial of patients with a mean left ventricular ejection fraction of >32.8% (CAPRICORN).

Key Question 1e. For adult patients with heart failure, do beta blockers differ in efficacy or effectiveness?

Direct comparisons

There were no direct comparator trials comparing 2 or more of the drugs proven to reduce mortality (bisoprolol, carvedilol, and sustained release metoprolol succinate). In the COMET trial, carvedilol was superior to metoprolol tartrate reducing all-cause mortality (number needed to treat, 18) after a mean follow-up of 58 months in patients with mild to moderate heart failure. No differences were found between carvedilol and metoprolol tartrate in improving symptoms (quality of life; New York Heart Association classification) or exercise capacity in 4 smaller head-to-head trials. Improvements in New York Heart Association function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol.

Placebo-controlled trials

Bisoprolol, metoprolol succinate, and carvedilol have each reduced total mortality, as a planned primary endpoint, by approximately 35%. Based on findings from the COPERNICUS trial (N=2289), carvedilol is designated as the beta blocker with the most direct, strongest evidence of having a mortality benefit in patients with severe heart failure. In a post-hoc subgroup analysis of 795 patients from the good-quality MERIT-HF trial, metoprolol succinate has also demonstrated a mortality reduction relative to placebo similar to that for carvedilol in patients who had a similar mortality risk.

In the SENIORS trial (N=2128), which involved patients who were, overall, older (mean age of 76 years) and healthier than in the prior major trials (higher mean left ventricular ejection fraction, lower annual placebo mortality rate), nebivolol was superior to placebo in reducing the risk of the primary composite outcome of all-cause mortality or cardiovascular hospital admission (31.1% compared with 35.3%; HR, 0.86; 95% CI, 0.74 to 0.99). When components of the primary outcome were examined individually as secondary outcome measures, differences between nebivolol and placebo were no longer statistically significant.

We found no trials that directly evaluated the effects of carvedilol phosphate, the long acting form of carvedilol, on mortality in adults with heart failure. Approval of the heart failure indication for carvedilol phosphate was based on "equivalence of pharmacokinetic and pharmacodynamic parameters between carvedilol phosphate and conventional carvedilol tablets."

Key Question 1f. For adult patients with atrial arrhythmia, do beta blockers differ in efficacy or effectiveness?

Direct comparisons

There were no differences between bisoprolol 10 mg and carvedilol 50 mg in preventing relapse of atrial fibrillation in patients subjected to cardioversion of persistent atrial fibrillation (> 7 days).

Placebo-controlled trials

Atenolol, nadolol, and pindolol, but not labetalol, were effective in controlling the ventricular rate, while labetalol was no more efficacious than placebo based on findings from a good quality systematic review examining 12 studies of rate control in patients with chronic atrial fibrillation. One placebo-controlled trial found that metoprolol CR/XL 100 to 200 mg was effective in preventing relapse of atrial fibrillation/flutter after cardioversion. Over 6 months, atrial fibrillation or flutter relapse rates were significantly lower in patients taking metoprolol CR/XL. Death rates were similar. The study was not powered to examine mortality.
A study examining the effects of carvedilol in managing patients with concomitant atrial fibrillation and heart failure found that when added to digoxin, carvedilol significantly improved mean left ventricular ejection fraction scores and reduced severity of symptoms/functional capacity when compared to digoxin alone. There were no differences between monotherapies of carvedilol or digoxin.

Key Question 1g. For adult patients with migraine, do beta blockers differ in efficacy or effectiveness?

Direct comparisons

Six head-to-head trials show no difference in efficacy in reduction of attack frequency, severity, headache days or acute tablet consumption, or in improvement in any subjective or composite index in any of the comparisons made (atenolol or metoprolol durules or metoprolol or timolol compared with propranolol or nebivolol compared with metoprolol).

Placebo-controlled trials

Results from placebo-controlled trials on similar outcome measures generally supports those for atenolol, metoprolol durules, and propranolol seen in head-to-head trials. Placebo-controlled trial results also show that bisoprolol had a significant effect on attack frequency reduction and that pindolol had no appreciable effects.

Key Question 1h. For adult patients with bleeding esophageal varices, do beta blockers differ in efficacy or effectiveness?

Direct comparisons

One small head-to-head trial showed no difference between atenolol and propranolol in rates of non-fatal/fatal rebleeding and all-cause mortality.

Placebo-controlled trials

Results of 1 trial of nadolol and 8 small placebo-controlled trials of immediate release and 2 formulations of extended release propranolol do not provide any additional indirect evidence of the comparative efficacy across beta blockers in these clinical outcomes. The somewhat mixed results across the placebo-controlled trials of propranolol suggest that treatment initiation interval may have an effect on rebleeding rates.

Key Question 2. Do beta blocker drugs differ in safety or adverse effects?

Side effects are common among patients taking beta blockers. In longer-term trials (12 to 58 months) directly comparing beta blockers in patients with hypertension (atenolol compared with bisoprolol compared with propranolol), heart failure (carvedilol compared with metoprolol), bleeding esophageal varices (atenolol compared with propranolol), or atrial fibrillation (bisoprolol compared with carvedilol), a few differences in specific adverse events were noted. But, overall, no particular beta blocker stood out from the others as being consistently associated with a significantly less favorable adverse effect profile.

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one beta blocker is more effective or associated with fewer adverse effects?

There is no data that suggests that any beta blocker is superior in any subgroup of patients based on demographics, other medications, or comorbidities.

SUMMARY

Results of this review are summarized below in Table 2.

Table 2. Strength of the evidence

	Strength of evidence[a]	Conclusion
Key Question 1. Comparative efficacy		
a. Hypertension	Overall grade: Poor	No head-to-head trials of long-term (≥6 months) health or quality-of-life outcomes. Reliable indirect comparisons cannot be made by evidence from 3 long-term placebo-controlled trials of propranolol and atenolol.
b. Angina	Overall grade: Fair	No significant differences in 6 head-to-head trials of carvedilol compared with metoprolol, pindolol compared with propranolol, betaxolol, and propranolol, and betaxolol compared with metoprolol in patients with stable angina. Atenolol equivalent to bisoprolol in patients with chronic stable angina and chronic obstructive pulmonary disease. Atenolol equivalent to labetalol when added to chlorthalidone in patients with chronic stable angina. One short-term, placebo-controlled trial of propranolol did not add any meaningful evidence of comparative efficacy in the above parameters.
c. Status-post coronary artery bypass graft	Overall grade: Poor	Metoprolol did not benefit mortality or ischemic events in a longer-term (>7 days) placebo-controlled trial (MACB).

	Strength of evidence[a]	Conclusion
d. Recent myocardial infarction	Overall grade: Fair-good	One fair-quality head-to-head trial found no differences in mortality after 1 year between atenolol and propranolol, but this was a relatively small trial; 1 fair-quality head-to-head trial found no differences in time to serious cardiovascular events between carvedilol and atenolol. One fair-quality trial of carvedilol and metoprolol tartrate found no differences in time to first cardiac adverse event or all-cause mortality. Similar mortality reductions reported for acebutolol, metoprolol tartrate, propranolol, and timolol in placebo-controlled trials of patients following myocardial infarction without other complications. Similar reductions in sudden death and reinfarction were reported for metoprolol tartrate and timolol and in sudden death for propranolol. No studies of carvedilol phosphate (extended-release carvedilol) in patients with recent myocardial infarction were identified. Carvedilol reduced mortality and reinfarction in 1 placebo-controlled trial of patients with a mean left ventricular ejection fraction of <32.7% (CAPRICORN). Four systematic reviews were not designed to assess comparative efficacy.
e. Heart failure	Health outcomes in head-to-head trials: Fair	Carvedilol more effective than metoprolol tartrate in reducing total mortality in COMET in patients with mild to moderate heart failure.
	Symptoms in head-to-head trials: Good	Carvedilol equivalent to metoprolol tartrate in improving symptoms (quality of life; NYHA) and exercise capacity in 4 head-to-head trials. Improvements in NYHA function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol.
	Placebo-controlled trials in mild-moderate heart failure: Good	Metoprolol succinate reduced total mortality, sudden death, and death due to progressive heart failure and improved quality of life (MERIT-HF). Carvedilol reduced total mortality, sudden death, and death due to pump failure (MOCHA). Nebivolol significantly reduced the composite outcome of all-cause mortality or cardiovascular hospital admission, but had nonsignificant effects each component as individual secondary outcomes. Bisoprolol reduced total mortality and sudden death. No studies of carvedilol phosphate (extended-release carvedilol) in patients with mild to moderate heart failure were identified.

	Strength of evidence[a]	Conclusion
	Placebo-controlled trials in severe heart failure: Fair for carvedilol and Fair for metoprolol succinate	Carvedilol reduced mortality and the combined endpoint of mortality and hospitalizations in a prospective trial. A post-hoc subgroup analysis of MERIT-HF suggests that metoprolol succinate is similarly effective in comparable patients. No studies of carvedilol phosphate (extended-release carvedilol) in patients with severe heart failure were identified.
f. Atrial arrhythmia	Overall grade: Fair	Bisoprolol equivalent to carvedilol in preventing relapse of atrial fibrillation in a head-to-head trial. Metoprolol succinate reduced incidence of atrial arrhythmia/fibrillation in a placebo-controlled trial. Carvedilol reduced 24-hour ventricular rate in patients with atrial fibrillation and heart failure in 1 placebo-controlled trial. These placebo-controlled trials did not offer comparative data.
g. Migraine	Overall grade: Fair	Atenolol, slow release metoprolol, immediate release metoprolol, and timolol were all similar to propranolol in their effects on pain outcomes and acute medication use in 5 head-to-head trials. No significant differences were found between nebivolol and metoprolol on frequency of migraine attacks and severity.
h. Bleeding esophageal varices	Overall grade: Poor	Results of 1 head-to-head trial of atenolol and propranolol, 1 placebo-controlled trial of nadolol, and 6 placebo-controlled trials of immediate release and 2 formulations of extended release propranolol, all fair quality, didn't clearly differentiate one beta blocker from another.
Key Question 2. Adverse effects		
Hypertension, stable angina, heart failure, atrial arrhythmia, migraine, bleeding esophageal varices, previous myocardial infarction	Overall grade: Fair	A few differences in specific adverse event rates were noted across longer-term trials directly comparing one beta blocker to another. Overall, no particular beta blocker stood out from the others as being consistently associated with a less favorable adverse effect profile.
Key Question 3. Subgroups		
a. Demographics (age, gender, race)	Overall grade: Fair	Evidence showed that age, gender, and race did not impact the effectiveness of carvedilol, immediate and controlled release metoprolol, and propranolol. There was insufficient evidence on the effect of beta blockers on perinatal mortality or preterm birth based on 1 systematic review.

	Strength of evidence[a]	Conclusion
b. High risk populations	Overall grade: Fair	*Heart failure.* Subgroup analyses of placebo-controlled trials showed that a history of myocardial infarction may reduce the protective effect of bisoprolol on mortality (CIBIS). No risk factor was found to confound the protective effect of carvedilol (COPERNICUS) or controlled release metoprolol (MERIT-HF) on mortality. *Post-myocardial infarction.* The MIAMI trial found that metoprolol had the greatest protective effect on mortality in patients with numerous risk factors. The BHAT trial found no variation in propranolol's protective effect on total mortality based on history of heart failure. *Diabetes.* Subgroup analysis of the SHEP trial found that the addition of atenolol to chlorthalidone did not significantly affect mortality relative to placebo. Metoprolol use reduced all-cause mortality and hospitalizations relative to placebo in a subgroup analysis of the MERIT-HF trial.

Abbreviations: NYHA, New York Heart Association classification.
[a] Quality of evidence ratings based on criteria developed by the Third United States Preventive Services Task Force.